REMARKS

Claims 15 – 23 and 25 – 29 are currently pending. Of these, claims 19 and 26-28 were previously set aside in response to a restriction requirement issued March 6, 2008. Claims 15, 16, and 17 are the pending independent claims. Claims 19 and 26-28 are therefore not currently being pursued, but they also have not yet been cancelled. Applicants may agree to do so upon receipt of a Notice of Allowance with regard to other claims if the restriction is not withdrawn.

Claims 15 – 18, 20 – 25, and 29 stand rejected under 35 U.S.C. § 103(a) based on Pulvirenti et al. (Journal of Pharmacology and Experimental Therapeutics, 1998) (hereinafter, "Pulvirenti 1998") in view of Glavan (Molecular Pharmacology, 2002) (hereinafter, "Glavan") in further view of Pulvirenti et al. (TiPS, 1994) (hereinafter, "Pulvirenti 1994").

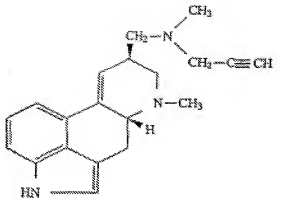
Each of the foregoing rejections is respectfully traversed and favorable reconsideration is requested in view of the following remarks.

I. Status of Claim 29

As a point of order, Applicants note initially that the recent Office Action stated "[c]laim(s) 15-18, 20-25, and 29 are examined herein insofar as they read on the elected invention and species." Applicants were under the impression claim 29 had been set aside, at least for now, as drawn to what was said to be a non-elected species (Group III) pursuant to the Office Action of March 6, 2008. It is requested that the Examiner clarify the status of claim 29.

II. The § 103(a) Rejections of Claims 15-18, 20-22, and 24-26

All of the pending independent claims (15 - 17) are directed to aspects of methods for the treatment of psychostimulant addiction and/or symptoms associated with psychostimulant. These claims require, *inter alia*, administering to the patient a pharmacologically acceptable form of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline (referred to in the application, and hereinafter, as "LEK-8829") as a partial dopamine agonist. A figure showing an embodiment of LEK-8829 is provided below for convenience.



Importantly, LEK-8829 is said to be a derivative of ergoline, but *it is not an aminoergoline*.

The Examiner contends that the Pulvirenti references teach the general usefulness of partial dopamine agonists in the treatment of pyschostimulant addiction. However, the Examiner acknowledges LEK-8829 is not mentioned in Pulvirenti, and it is evident that Pulvirenti only makes specific mention of terguride as one agonist that "may" be useful. In regard to the specific compound LEK-8829 claimed by Applicants, the Examiner cites Glavan, which is said to disclose that LEK-8829 is a partial dopamine agonist. In view of this characterization of LEK-8829, the Examiner argues it would have been obvious from Pulvirenti to try to use LEK-8829 to treat pyschostimulant addiction. It is respectfully submitted that this is not a proper application of the law of obviousness, and that Applicants' claims do indeed patentably distinguish over the cited art.

Pulvirenti 1994 states in reference to terguride that it may be "*reasonable* to *speculate* that partial agonists at dopamine receptors *may* also be useful during withdrawal from cocaine and amphetamine" and that "it is *possible* that dopamine receptor partial agonists *may* represent *potential candidates* for normalizing dopamine neurotransmission during the various phases of the natural history of psychostimulant addition." *See* Pulvirenti 1994, page 377 (emphasis added). However, this is expressed with such reservation that it is evident that the authors had very little certainty with respect to whether some, most, or only a handful of the broad class of

partial dopamine agonists would actually be useful as a medicament for treatment of psychostimulant addiction.

A statement this vague and ambiguous can hardly be said to be a suggestion that the specific compound LEK-8829 would be expected to be useful in the treatment of withdrawal symptoms from psychostimulant addiction. One speculative, vague comment that a particular member of a broad class of compounds "might" help in the treatment of some human condition cannot reasonably be said to foreclose the patentability of any/all later discoveries of beneficial effects of other specific and different compounds in that broad class. The Examiner's argument proves too much. It takes "obvious to try" entirely too far. It is not the intent of Section 103 to foreclose patent protection for an entire field of technological advance based on speculation about the usefulness of one species in a broad class of compounds with unpredictable pharmacological properties.

Pulvirenti focused their studies on a specific subclasss of partial dopamine agonists, namely, aminoergolines. In particular, Pulvirenti studied the aminoergolines terguride, SDZ208911 and SDZ208912. Pulvirenti did not randomly select other non-aminoergoline partial dopamine agonists to see if these compounds "might" also be effective in the treatment of psychostimulant addiction.

The upshot, then, of the Pulvirenti references is that if one wishes to determine compounds that would be effective in the treatment of psychostimulant addiction, he or she might want to focus on aminoergolines structurally similar to the tergurides, SDZ208911 and SDZ208912. But the LEK-8829 compound disclosed in Glavan and the one called for in the present claims is *not* an aminoergoline. In aminoergolines, such as terguride, SDZ208911 and SDZ208912, a -NH-CO- is bonded to the ergoline skeleton at the 8 beta location. In other words, the egroline skeleton is directly bonded to the nitrogen atom of the amine group. In contrast, LEK-8829 has substantially different chemical structure which includes a methylene group at the 8 beta position of the ergoline skeleton as shown in the structure above.

Given Pulvirenti's speculative comment about a possible use for one category of compounds from the broad class of partial dopamine agonists, a person of ordinary skill in the art considering the Pulvirenti references "might" be encouraged to try one of the tergurides for treating psychostimulant addiction, but nothing in this speculative comment would make it "obvious" to try any/all other partial dopamine agonists for this purpose with an expectation of

success and, as a result, foreclose patent protection for all species of compounds in the class that ultimately prove beneficial. Considering the vast number of chemical species in play, it would certainly not be "obvious to try" LEK-8829 for treatment of this condition based on the speculative comments of Pulvirenti 1994 and Pulvirenti 1998 in regard to the "potential" usefulness of a different category of compounds in the same broad class. Thus, the combination of Pulvirenti 1994 with Pulvirenti 1998 cannot lawfully be said to render the use of LEK-8829 obvious for the treatment of psychostimulant addiction.

Even with Glavan added to the mix, a person of ordinary skill would not have viewed it as obvious to use or even try to use LEK-8829 for the treatment of psychostimulant addiction. Again, LEK-8829 is not an aminoergoline, and is substantially different in chemical structure from aminoergolines such as terguride, SDZ208911 and SDZ208912, mentioned in Pulvirenti as specific ergolines that "might" work. The mere mention of LEK-8829 in Glavan would plainly not have lead one of ordinary skill in the art to see LEK-8829 as a viable alternative to aminoergolines in the treatment of psychostimulant addiction.

Glavan itself discloses LEK-8829 to be an *experimental anti-psychotic* medicament. Glavan makes no mention of the use of LEK-8829 for treatment of psychostimulant addiction. With all due respect, there is no valid basis to combine Glavan with Pulvirenti 1994 and/or Pulvirenti 1998 to deny the patentability of Applicants' claims without improperly arranging such a combination from the convenient but impermissible perspective of hindsight. *See* MPEP § 2145 (A).

An obviousness rejection based upon an 'obvious to try' rationale is limited to circumstances where one skilled in the art is choosing from a *finite number* of identified, *predictable* solutions, with a *reasonable expectation of success*." MPEP § 2145 (X)(B) (emphasis added). It is very plan that these factors are not present is the case at hand. In particular, the class of all possible partial dopamine agonists is open-ended. As more partial dopamine agonists are discovered by researchers, this class of compounds continues to grow larger and larger. Consequently, the class of all partial dopamine agonists is simply too large to reasonably (or lawfully) conclude that it would have been obvious to try all of the members of the class.

Additionally, the members of the large class of partial dopamine agonists differ significantly from one another, and their full and comparative effectiveness (and side-effects)

in many respects are known to be unpredictable. One of ordinary skill could not have had a reasonable expectation from Pulvirenti or any known prior art or combination thereof that all partial dopamine agonists, such as LEK-8829, would be effective in the treatment of psychostimulant addiction, just because Pulvirenti speculated that one category of compounds from the general class "might" be.

The variability of the effectiveness of such drugs is exemplified in U.S. Patent No. 5,288,724 to Rucman et al. As noted in the Applicants' specification, the Rucman patent discloses LEK-8829, along with other structurally similar ergoline derivatives. Notably, none of the ergoline derivatives in Rucman is an aminoergoline. Despite the apparent structural similarity of Rucman's ergoline derivatives, Rucman reports that the pharmacological activity of these compounds (vasoconstriction, uterotonic activity, pupil dilatation, etc.) varied profoundly. *See*, generally, Col. 6 – 9 of the '724 patent. As between LEK-8829 and the aminoergolines mentioned in the Pulvirenti references (terguride, SDZ208911 and SDZ208912), even more variability in pharmacological activity would have been expected.

Consequently, the general class of partial dopamine agonists is simply (1) too large and (2) too unpredictable to reasonably (or lawfully) conclude that the use of LEK-8829 would have been obvious to try simply because one or two combined references (i.e., Pulvirenti 1994 and Pulvirenti 1998) speculate that certain specific sub-categories of the broad class of partial dopamine agonists in the form of aminoergolines *may* be useful for the treatment of psychostimulant addiction. Again, LEK-8829 is not an aminoergoline. Assuming *arguendo* a person having ordinary skill in the art would follow-up on the speculative comments in Pulvirenti 1994 and Pulvirenti 1998, and there is no reason to suppose they would, such a person would be experimenting on aminoergolines (and would be occupied for a long time doing so because of the size and complexity of aminoergolines). Glavan does nothing to bridge the gap between the aminoergolines mentioned in Pulvirenti and the structurally different LEK-8829 compounds claimed by Applicants, or lead a person having ordinary skill in the art to try to use LEK-8829 as a medicament for treating psychostimulant addiction. If anything, Rucman and similar references would dissuade one from such an adventure.

Finally, it is noted that Claim 15 has been amended herein to specify that the LEK-8829 is administered in a therapeutically effective amount, which is from about 0.05 to about 20 mg. This dosage range is not specified in either Pulvirenti 1994, or Pulvirenti 1998, or Glavan. In

fact, while the three references disclose dosage rates for testing in rats, none of three references discloses any dosage rates for using in human patients. Thus, this limitation provides an additional ground for patentably distinguishing Claim 15 (and its dependent claims) over the cited references.

In light of the arguments set forth above, Applicants respectfully assert the combination of Pulvirenti 1994, Pulvirenti 1998, and Glavan does not lawfully render claims 15 – 17 obvious under § 103(a). Accordingly, claims 15 – 17 patentably define over Pulvirenti 1998 in view of Glavan in further view of Pulvirenti 1994. Reconsideration and allowance of claims 15 – 17 are respectfully requested. Likewise, their dependant claims patentably define over the cited references for at least the same reasons.

In light of the foregoing, Applicants respectfully request the Examiner reconsider the application, withdraw the rejections, and issue a notice of allowance at the earliest possible convenience.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 12-2355.

Respectfully submitted,

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